REMARKS

This amendment resubmits the amendments in the unentered Amendment in Response to Advisory Action and includes the changes in claim 128 suggest by Examiner Webman.

Withdrawal of the Rule 75 objections is respectfully requested. Uterine bleeding and breakthrough bleeding are not synonymous. Likewise, antimitotic activity and inhibition of endometrial growth are not the same. Accordingly, the two sets of claims, in both instances, are not duplicates and do not have the same scope.

The provisional non-statutory double patenting rejection does not require any response. However, it is noted that this case will be in condition to be allowed after this response is filed and the copending application will still be on appeal. Under PTO procedure applicable to that circumstance, that rejection will be transferred to the other case, to the extent appropriate, and withdrawn here.

The rejection of claims 31-66 and 127 under 35 USC § 112, second paragraph is respectfully traversed.

There is nothing indefinite or unclear about the scope of claims 61-65, all of which cover a dosage of 1-10 mg/kg. Claim 66 is dependent on claim 61 and clearly covers the situation where the person's weight (e.g., 50 kg or 110 pounds) is such that 1-10 mg/kg corresponds 50-500 mg in absolute terms. Claim 66 is therefore also not indefinite.

Claim 127 is dependent on claim 108 which refers to administration of antiprogestin. That provides sufficient antecedent basis for a period of such administration.

All claims have been rejected over Ortmann in view of Casper. Those rejections are respectfully traversed.

Ortmann's opening background paragraph, noted by the Examiner, mentions that RU 486 causes menstrual bleeding, which makes it useful as a drug for fertility control. HRT is not mentioned there or elsewhere in the article, and therefore, there is no suggestion of the use of antiprogestin in HRT.

Moreover, it must be kept in mind that Ortmann presents and comments on studies of rat pituitary cells exposed to various combinations of estrogen, progestin, and antiprogestin whereas the presents invention concerns the use of antiprogestins to control

the human endometrium. The effects of anti-progestins are heterogeneous between these tissues and across these species. Therefore, one cannot conclude that the actions of antiprogestins in pituitary cells will apply to the endometrium, nor can one assume that the effects on rat cells will be relevant to human tissues. In that connection, note that Ortmann distinguishes his results from that in humans on page 295, column 1, line 3 to 10, and states that in vivo in the human, RU486 did not reverse the inhibitory action of progestin on LH and FSH levels. Further, on page 295, column 1, paragraph 2, Ortmann details the lack of consistency on the effect of RU486 on LH and FSH secretion. Still further, Ortmann teaches on page 295, column 2, paragraph 3 that the inhibitory effects of RU486 are via a non-specific or toxic effect. In contrast, the work underlying this patent application demonstrates that the inhibitory effect of antiprogestin on the endometrium is a non-competitive anti-estrogenic effect via action through the progestin receptor to inhibit the estrogen receptor, not via progestin antagonism, but by a direct molecular mechanism involving the interaction of the anti-progestin with the progestin receptor. Ortmann on page 295, paragraph 3 teaches that the RU486 effect cannot be a blocking of the sensitizing effect of estradiol given that RU486 does not bind to the estrogen receptor, but in the endometrium, Hodgen has shown that RU486 does block the action of the estrogen receptor, through the antiprogestin's binding to the progestin receptor.

Casper relates to contraception or HRT using estrogen and progestin such that the dominant activity of these hormones alternates. It does not concern the use of antiprogestins, and like Ortmann, does not suggest any type of use of antiprogestin in HRT.

Since neither reference teaches or suggests the use of antiprogestin in HRT, the obviousness rejection is clearly untenable. Nevertheless, it is contended on page 7 of the Office Action that based on Ortmann and Casper, one would have been motivated to combine an antiprogestin because it is a contraceptive and would induce scheduled bleeding and therefore reduce the incidence of breakthrough bleeding. The basis for this assertion that menses reduces bleeding during the inter-period time is made without any citation of authority. In any event, while high dose antiprogestin treatment induces menstruation, that is a different process than identified by Hodgen in which antiprogestin induces endometrial atrophy through blockade of the estrogen receptor by the binding of the antiprogestin to the progestin receptor.

While it is asserted that the antiprogestin "would act as a progestin agonist and reduce the development of endometrial atrophy caused by the administration of progestin as taught by Casper", this invention is exactly the opposite; the antiprogestin treatment

induces endometrial atrophy, thus ameliorating the problems of breakthrough bleeding and spotting that occur with estrogen alone or estrogen and progestin hormone replacement therapy in post-menopausal women. Ortmann teaches on page 295, column 2, that RU486 acts as a progestin agonist on the human endometrium. A discovery underlying the present invention is that RU486 induces endometrial atrophy via inhibition of the estrogen receptor through RU486's binding to the progestin receptor.

Further, the contention that "estrogen and progestin administration can be continued uninterrupted as taught by Casper since breakthrough bleeding would no longer be an issue" is not valid since that conclusion is not justified by the language "may avoid the problem of withdrawal [not breakthrough] bleeding" or "may be associated with breakthrough bleeding". In actually fact, breakthrough bleeding and spotting in post-menopausal women on estrogen alone or estrogen and progestin hormone replacement therapy is a problem. The Hodgen invention, (i.e. the use of intermittent or continuous antiprogestin to induce endometrial atrophy) will ameliorate this breakthrough bleeding and spotting problem well known to be associated with hormone replacement therapy in post-menopausal women.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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